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Mass in the neck after radiation exposure from Chernobyl disaster

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A 55-year-old white man in good health underwent a thorough triennial physical examination, and a mass in the left neck was found on a multidetector computed tomography (CT) scan of the heart and vessels in the chest and abdomen. He was referred to an otolaryngologist, who ordered magnetic resonance imaging, and was sent for evaluation and treatment.

The patient had rock-hard masses in the left and right sides of the neck and at the junction of the right lobe and isthmus of thyroid. Further review of his heart CT scan showed mediastinal lymphadenopathy *(Figure 1)*. He reported no personal or family history of thyroid problems. He also reported no history of irradiation—although then he queried: "Does it matter that we lived in Norway when Chernobyl blew up?"

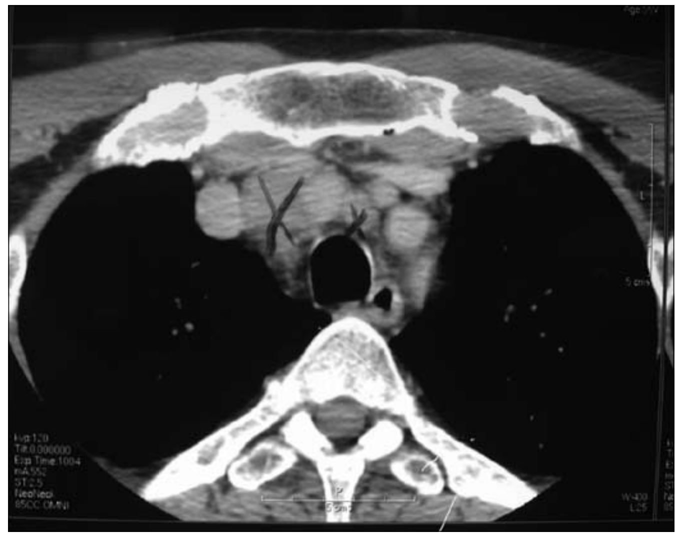

Figure 1. A CT scan with dye showing mediastinal lymphadenopathy.

The Chernobyl nuclear reactor accident occurred on April 26, 1986, in what is now northern Ukraine. Reactor number 4 exploded; further explosions and the resulting fire sent a plume of highly radioactive fallout into the atmosphere and over an extensive geographical area *(Figure 2)*. Although Norway is about 1200 miles away from the disaster site, the combination of precipitation and a large initial thermal lift caused about 3% to 5% of the radiocesium to be deposited in that country (1). Our patient, an American working for an oil company in Norway, lived in the coastal region—away from the central mountainous region in Norway that was primarily affected—and received an estimated radiation dose of 2 to 10 KBq. Overall, the fallout from the Chernobyl disaster was 400 times that of the atomic bombing of Hiroshima, and the average effective doses individuals accrued over a 10-year period from external exposure and ingestion varied from 0 mSv in some areas in Europe to 10 mSv in areas close to the explosion site (2).

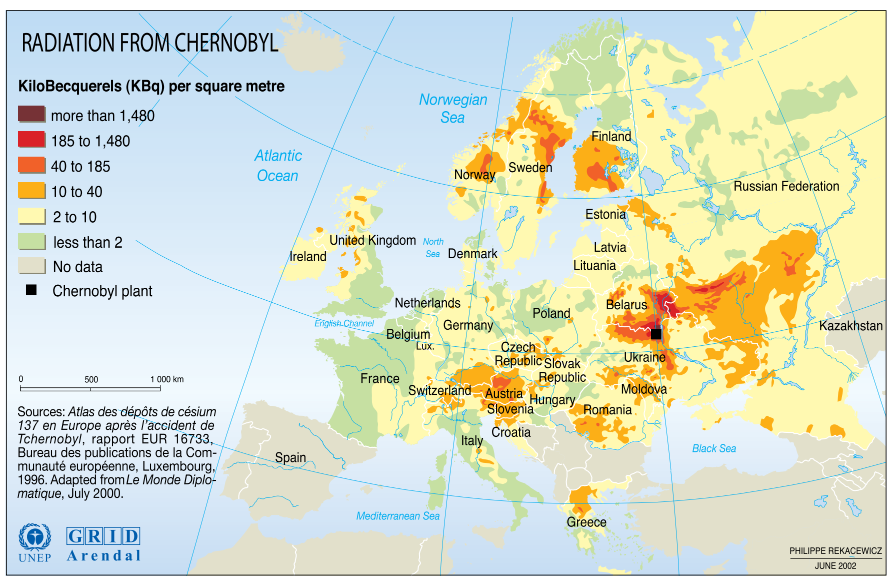

Figure 2. Radiation from Chernobyl. Reprinted with permission from the United Nations Environment Programme.

A fine-needle aspiration biopsy of the right lobe of the thyroid was done in the office, and results showed papillary thyroid carcinoma *(Figure 3)*. A week later, the patient underwent a total thyroidectomy with bilateral modified radical neck dissections, a central compartment dissection (level

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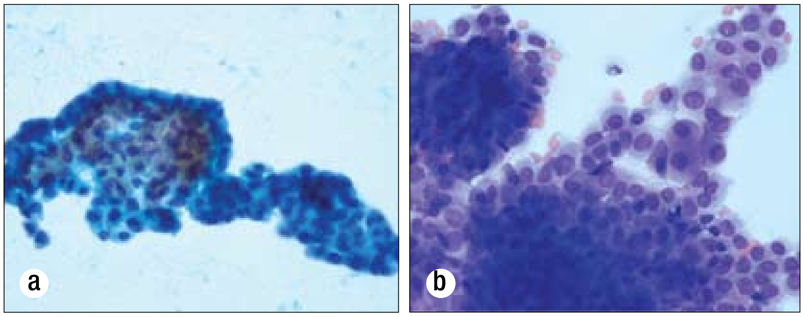

Figure 3. Cytological specimen from a fine-needle aspiration biopsy of the right lobe of the thyroid. **(a)** Clusters of atypical cells with moderate nuclear pleomorphism (Papanicolaou stain, 100×). **(b)** A higher-power view of the atypical cell population showing increased nuclear to cytoplasmic ratios, nuclear pleomorphism, nuclear pseudoinclusions, and ground-glass chromatin (Diff-Quik stain, 400×).

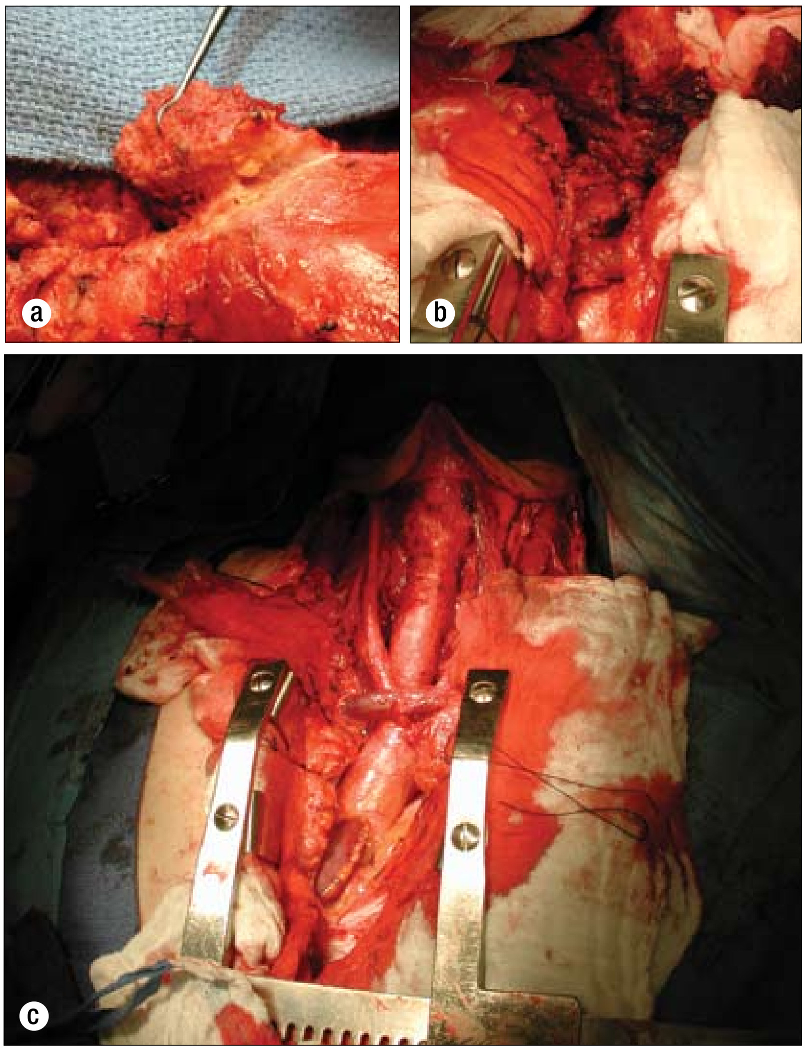

Figure 4. The total thyroidectomy, with a bilateral modified radical neck and mediastinal dissection, showing **(a)** tumor adhering to the cricoid, **(b)** mediastinal disease, and **(c)** the mediastinum after removal of the nodes, demonstrating the extent of resection.

VI), and a mediastinal dissection (level VII) through a sternal split, with a sternohyoid myoplasty flap.

At the time of surgery, the tumor was densely adherent to the anterolateral area of the right side of the cricoid cartilage and the first two tracheal rings, requiring an extensive dissection. Both recurrent laryngeal nerves were encased in adenopathy, which was very hard and clinically contained metastatic thyroid cancer. Because his vocal cords were moving prior to the initiation of surgery, the nerves were dissected from within the surrounding nodes from the inferior border of the cricothyroid muscle down to the subclavian vessels. Direct laryngoscopy at the termination of the procedure showed that both cords were moving, with the right more than the left. The 7½-hour procedure was extremely difficult due to the extensive nature of the cancer and the fact that the recurrent laryngeal nerves were completely encompassed by nodes containing cancer *(Figure 4)*.

Figure 5. Tissue from the total thyroidectomy, bilateral modified radical neck dissections, and a mediastinal dissection. The overall specimen dimensions were 16.0 × 14.3 × 2.3 cm. The thyroid portion of the specimen measured 7.9 × 8.4 × 2.3 cm.

On gross pathological exam *(Figure 5)*, the cancer appeared to involve the entire thyroid and was found in the nodes bilaterally, with involvement on the left being greater than the right. The entire isthmus region was replaced by matted lymph nodes and tumor. Microscopically, there was bilateral well-differentiated papillary carcinoma of the thyroid with extracapsular extension *(Figure 6)*. Multifocal, microscopic tumor extension to the margins of resection was present, as well as multifocal foci of vascular and lymphatic invasion. The tumor invaded the sternocleidomastoid muscle and the tissue overlying the cricoid cartilage. Forty-three of 81 nodes had evidence of metastatic disease *(Figure 7)*. In some areas, the tumor had a more columnar appearance with elongated nuclei, suggesting areas with tall-cell variant differentiation. This is important due to the increased aggressive behavior of tumors with this type of differentiation. Thyroid tumors with tall-cell differentiation more commonly have extracapsular extension, lymph node metastasis, and hematogenous spread. Usually, this histologic variant is seen in individuals >60 years of age (3). Based on the pathological results, the disease was T_{4A}, N_{1b}, M_o, or stage IVA.

In the immediate postoperative period, the patient had a left Horner's syndrome and temporary hoarseness that lasted 8

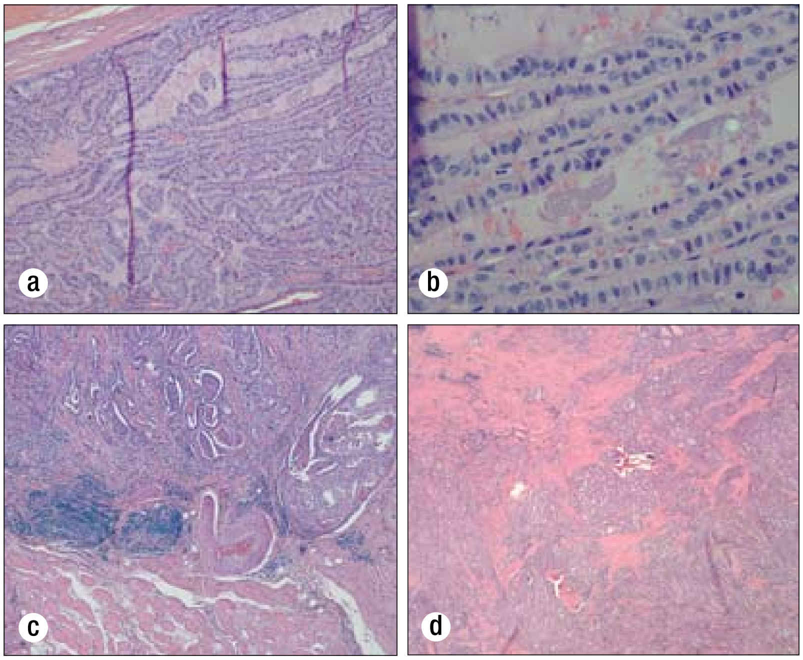

Figure 6. Hematoxylin and eosin–stained slides of the tumor. **(a)** Elongated papillary projections with mild nuclear pleomorphism, nuclear grooves, increased nuclear to cytoplasmic ratio, and scant colloid (100×). **(b)** Higher-power view showing some areas with columnar-type cells, nuclear pleomorphism, and elongated nuclei, suggesting that some areas of the tumor contain the tall-cell variant of papillary thyroid carcinoma (400×). **(c)** Tumor invading the sternocleidomastoid muscle (40×). **(d)** Tumor invading the soft tissue overlying the cricoid cartilage (40×).

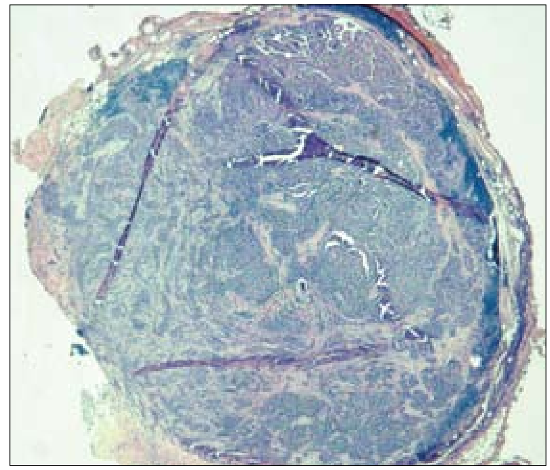

Figure 7. Tumor in the lymph node overlying the recurrent laryngeal nerve (hematoxylin and eosin stain, 40×).

Figure 8. (a) Preoperative and **(b)** postoperative CT scans of the neck and chest; the postoperative scan shows removal of the x-marked node.

weeks, but his serum intact parathyroid hormone (PTH) level was normal. Postoperative CT scans of the neck and chest showed that all gross disease had been removed *(Figure 8).* He was placed on levothyroxine replacement, since treatment with radioactive iodine (RAI^{131}) would be delayed for 6 weeks due to the CT scans with iodine dye. We felt that the information obtained regarding the extent of cervical and mediastinal nodes outweighed the potential from possible problems due to this delay of RAI^{131} treatment. Following this, external beam radiation using an intensity-modulated radiation therapy technique with sensitizing Adriamycin was planned. Adriamycin would also be given prior to the RAI^{131} dose.

DISCUSSION

While thyroid cancer is a relatively uncommon malignancy, it has the fastest rising incidence of malignancies in the USA, with an annual US incidence of about 37,000 cases (4). Nearly three fourths of new cases are in women, and three fourths of the cases can be classified as low risk (5). Our patient had a high-risk carcinoma, based on factors such as his age (papillary thyroid carcinoma diagnosed in patients >45 years has a worse prognosis), his gender (men tend to have poorer outcomes, although that trend may be related to a somewhat higher age at diagnosis), and advanced clinical stage.

The incidence of thyroid cancer has been rising rapidly, with a 310% increase between 1950 and 2004 (6). This rise is partially related to earlier detection but may also be linked to the use of radiation therapy to treat benign childhood conditions from 1910 to 1960 (7). Indeed, radiation exposure is the most prominent environmental factor associated with all tumors of the thyroid, which is a very radiation-sensitive organ. Increased rates of cancer have been associated with exposure to just 10 cGy (8) and have persisted for at least 4 decades after radiation exposure (9).

In 2006, the United Nations–led Chernobyl Forum reported that about 4000 cases of thyroid cancer had been linked to the Chernobyl disaster, of which 1% were fatal (10). Most of these cases were in children and adolescents. According to a review article in *The Lancet Oncology* (11), the evidence linking adult thyroid cancer with the Chernobyl disaster is not conclusive *(Table 1).* The susceptibility to radiation-induced cancer may be related to metabolic rate, as younger people with a lower metabolic rate absorb higher doses of radionuclides (12). It is also possible that a longer follow-up period is needed for increased rates of thyroid cancer to be apparent in adults

Table 1. Chernobyl-related exposure to ionizing radiation and risk of thyroid cancer in adults*

Ref	Country of study	Design	Study period	Type of comparison	Exposure variables	Key findings
Mettler et al, 1992	Ukraine	Descriptive (prevalence)	1990	Prevalence of thyroid nodules	Seven contaminated villages (>555 kBq/ m^2 of ^{137}Cs) vs six control villages (<37 kBq/m^2 of ^{137}Cs)	No difference in prevalence of thyroid nodules
Prisyazhniuk et al, 1995	Ukraine	Descriptive (incidence)	1980–1993	Incidence rates over time		No significant increase
Inskip et al, 1997	Estonia	Liquidator cohort (incidence)	1995	Prevalence of thyroid nodules	Questionnaire on work-related exposure; physical measurements	No difference in presence of thyroid abnormalities among liquidators with high and low exposures
Ivanov et al, 1997	Russian Federation	Liquidator cohort (incidence)	1986–1990	Incidence in cohort vs general population	Assigned doses of external irradiation, based on exposure during clean-up operation	Greater incidence among liquidators: SIR = 670; 95% CI 420–1030
Ivanov et al, 1997†	Russian Federation	Descriptive (incidence, mortality)	1981–1995	Incidence rates over time	Contaminated areas vs noncontaminated areas	No significant increase in contaminated areas vs noncontaminated areas
Rahu et al, 1997	Estonia	Liquidator cohort (incidence)	1986–1993	Incidence in cohort vs general population	Questionnaire on work-related exposure	No excess thyroid cancer incidence
Ivanov et al, 1999	Russian Federation	Descriptive (incidence)	1982–1995	Incidence rates over time	Contaminated areas vs noncontaminated areas	Greater number of thyroid cancers detected in contaminated areas between 1991 and 1995 vs 1986 and 1990

*Reprinted from Moysich et al, 2002 (11), from *The Lancet Oncology* with permission from Elsevier.

†Combination of two articles: one in *Br J Radiol* and one in *Radiat Environ Biophys.*

SIR indicates standardized incidence ratio; CI, confidence interval.

(11). At the time of the disaster, our patient was 33 years old. His two children were 5½ and 3½ then; both of them and the patient's wife were also screened with sonography and had no signs of thyroid cancer.

The Chernobyl Forum report attempted to put the health effects of the Chernobyl accident into perspective. It commented:

> Apart from the dramatic increase in thyroid cancer incidence among those exposed at a young age, there is no clearly demonstrated increase in the incidence of solid cancers or leukaemia due to radiation in the most affected populations. There was, however, an increase in psychological problems among the affected population. . . . It is impossible to assess reliably, with any precision, numbers of fatal cancers . . . or indeed the impact of the stress and anxiety induced by the accident and the response to it. Small differences in the assumptions concerning radiation risks can lead to large differences in the predicted health consequences, which are therefore highly uncertain (10).

Based on these data, it is not possible to say whether our patient's papillary thyroid carcinoma was linked to the Chernobyl disaster. Nevertheless, treatment recommendations for papillary thyroid carcinoma are the same regardless of whether a link to radiation exists. Surgery is the primary treatment for all patients. Most experts recommend total or near-total thyroidectomy when thyroid carcinoma has been diagnosed preoperatively (13, 14); studies have also noted the importance of having surgeons experienced in the technique to minimize treatment-related morbidity (14–16). Radioiodine is indicated for the great majority of patients; it is usually given for 4 to 12 weeks after surgery, both to destroy any remnant thyroid tissue and to identify (through imaging) and treat any metastatic disease (17). Hormone therapy, typically oral thyroxine, corrects the surgically created hypothyroidism and suppresses thyroid-stimulating hormone (TSH) (18). For patients with stage III and IV disease, the serum TSH level should be <0.1; for other patients, it should be low to normal, i.e., 0.1 to 0.2 mU/L (19).

Although no data support the general usefulness of adjunctive chemotherapy, doxorubicin may act as a radiation sensitizer (20, 21) and thus is an option for higher-risk patients who undergo external beam radiation (14). It may also be used palliatively in life-threatening cancers that have not responded to other forms of therapy (22). Data from retrospective studies support the role of external beam radiation in controlling gross and microscopic residual disease (23) *(Table 2),* as well as in

Table 2. Ten-year local recurrence rates after adjuvant external beam radiation therapy for high-risk disease*

Study	Treatment: Surgery with RAI (%)	Treatment: Surgery, RAI, and XRT (%)
Tubiana et al, 1985	21	14
Simpson et al, 1998	18	14
Philips et al, 1993	21	3
Farahati et al, 1996 (includes distant failures)	50	10
Tsang et al, 1998 (papillary only)	22	7
Kim et al, 2003 (papillary only, 5-year rates)	37.5	4.8
Keum et al, 2006	89	38
Brierley et al, 1996 (patients over 60 who have ETE)	34.3	13.6
Chow et al, 2002 (papillary only with T4a)	17.6	11.6

*From Brierley JD, Tsang RW, 2008 (23). Reprinted with permission from Elsevier.
RAI indicates radioactive iodine; XRT, external beam radiotherapy; ETE, extrathyroidal extension.

Table 3. Experimental agents for treatment of papillary thyroid carcinoma*

Category	Drug
Multitargeted kinase inhibitor	Axitinib Gefitinib Motesanib diphosphate (AMG-706) Sorafenib Sunitinib Vandetanib
Raf kinase inhibitor	XL281
Endothelial growth factor receptor inhibitor	Pazopanib hydrochloride
Histone deacetylase inhibitor	Vorinostat Valproic acid Depsipeptide
DNA methylation inhibitor	Decitabine
Heat shock protein-90 inhibitor	17-allyamino-170-demethyoxygel-danamycin (17-AAG)
Proteasome inhibitor	Bortezomib
Histone deacetylase inhibitor	Vorinostat
MEK inhibitor	AZD6244
Nuclear receptor agonist	Bexarotene Rosiglitazone
Cyclooxygenase inhibitor	Celecoxib
Monoclonal antibody	Trastuzumab plus R115777
Derivative of thalidomide	Lenalidomide

*Compiled from National Comprehensive Cancer Network guidelines (13), UpToDate (19), and ClinicalTrials.gov.

palliative treatment. New therapies are also emerging for papillary thyroid cancer and are in some phase of testing (*Table 3).*

Follow-up of the patient continues every 6 to 12 months after radioiodine ablation to assess local, regional, and distant control. Lower-risk patients are now usually monitored with neck ultrasound and measurement of serum thyroglobulin levels; patients at higher risk, such as our patient, require additional radioiodine scans and possibly other imaging, including positron emission tomography (13, 24). Fortunately, the prognosis for patients with papillary thyroid carcinoma is good. For example, in a 2008 study of 950 consecutive patients with papillary thyroid carcinoma, only 79 patients (8.3%) developed locoregional or distant metastases, and the overall survival rate was 91% at 10 years and 89% at 15 years (25). The 15-year survival rate was 98% for stage I, 96% for stage II, 85% for stage III, and 65% for stage IV (25).

Acknowledgments

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